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Review article

Extraction of bioactive compounds from pomegranate: A review

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A B S T R A C T

Increasing demands for health-promoting compounds originated from natural sources have led to a surge of interest in studies in the field of extraction and purification of such components to be used in the formulations of value-added foods. Pomegranate is a rich source for mining biologically active or bioactive ingredients such as phenolic compounds, tannins, and anthocyanins. These compounds have various bioactivities such as antioxidant, antimicrobial, and anticancer properties. However, extraction and purification of such compounds from different parts of the pomegranate as efficiently as possible is a challenging task usually carried out by solvent extraction, microwave-assisted extraction, and ultrasound-assisted extraction techniques. Therefore, in the present study, first the bioactive compounds of pomegranate are highlighted and then common methods used to extract them are reviewed.

Keywords: Pomegranate; Bioactive compounds; Extraction methods; Functional foods

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1. Introduction

Pomegranate (*Punica granatum* L.) is a fruit of the tree that has seeds that are often red, and sometimes white, or colors between the two. Its peel color is often red and sometimes black or almost yellow. Pomegranate is a fruit that grows in different regions such as Iran, the Middle East, Spain, India and the United States. This fruit is used in different ways, which include fresh fruit, juice, wine or jam (Seeram et al., 2005; Fazaeli et al., 2013). In different varieties of pomegranate, its pigments change from yellowish white to very bright red or dark red, and its juicy seeds are sweet, sour, very sour or smooth. The chemical composition of this fruit depends on the cultivar, growing area, climate, maturity, agricultural care, and storage conditions. According to the most historians, pomegranate is a native fruit of ancient Iran and then gradually spread from Central Asia to the Himalayas, the Middle East, Asia Minor, and the Mediterranean (Akhtar et al., 2015; Pirzadeh et al., 2020).

Pomegranate fruit has different therapeutic properties such as antioxidant, anti-cancer, and antimicrobial activity. In addition, pomegranate consumption is very useful in treating cardiovascular diseases (Youssefi et al., 2009; Moghadam et al., 2020). This fruit is rich in various bioactive compounds, including phenolic compounds, vitamins and carotenoids, which are very attractive sources of natural antioxidant compounds (Dadashi et al., 2013; Alexandre et al., 2017). This fruit consists of three parts: the seeds, which make up about 3% of the weight of the fruit and contain 20% of oil; Juice, which makes up about 30% of the weight of the fruit, and the peel of the fruit, which is attached to the seeds. Pomegranate fruit is consumed in the world in various forms including fresh or processed such as fruit juice, paste, kernel oil, vinegar, and pomegranate seeds (Malviya et al., 2014; Rajha et al., 2019).

Now, in order to use these biologically active compounds or to investigate their presence in different parts of pomegranate, it is necessary to extract and purify these compounds from the raw material or matrix of the product, which can be completed through different methods and techniques (Cam & Hisil, 2010; Yi et al., 2016). The most common methods to extract bioactive compounds from pomegranate are solvent extraction-based methods. Various solvents such as water, methanol, and ethanol have been employed for this purpose. However, today other methods such as pressure-based, microwave or ultrasonic methods are also employed to extract these bioactive compounds. In fact, the use of different methods leads to changes in the extraction process and results such as the amount of antioxidants in the produced compounds, the amount of extraction efficiency and the amount of total phenol of the extracted ingredients (Abbasi et al., 2008; Goula et al., 2017; Rajha et al., 2019). Therefore, the purpose of this study is to

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investigate the properties of bioactive compounds in pomegranate and also to investigate the different methods used to extract these compounds.

2. Bioactive compounds of pomegranate

Pomegranate is a natural source of phenolic compounds that contain antioxidants such as tannins, polyphenols, flavonoids, and vitamin C. Other pomegranate antioxidants include tocopherols and anthocyanins that have been shown to have prophylactic and therapeutic properties. Biochemical properties of these phytochemicals are often due to their reducing properties, which are known as reducing agents, hydrogen donors, single oxygen quenchers, and even molecules with the ability to chelate metal ions (da Silva et al., 2013; Sreekumar et al., 2014; Panth et al., 2017). Several chemical compounds have been isolated from different components of the pomegranate plant, the most important of which are as follows: peel: gallic acid, allagic acid, punicalin, punicalagin, caffeic acid, ellagitannins, luteolin, camphorol and quercetin. Juice: simple sugars, aliphatic acids, ellagic acid, quicic acid, flavonols, amino acids, minerals, and ascorbic acid. Roots and trunk skin: ellagi tannins and alkaloids. Flowers: gallic acid, ursolic acid, triterpenoids and fatty acids. Leaves: carbohydrates, reducing sugars, sterols, saponins, flavonoids, tannins, glycosides and ellagitannin. Seeds: punicic acid, oleic acid, palmitic acid, stearic acid, linoleic acid, sterols and tocopherols (Vucic et al., 2019). The structure of some of the most important bioactive compounds in pomegranate is shown in Fig. 1. These bioactives are divided into four main categories: hydrolyzable tannins, anthocyanins, phenolic compounds, and fatty acids.

However, most research in the food industry to extract bioactive compounds from pomegranate has focused on pomegranate seeds and peel. Pomegranate juice is also a rich source of polyphenolic compounds. Pomegranate seeds or kernels are also a rich source of oil, which makes up 12 to 20% of the seed weight. This oil is composed of approximately 80% of conjugated fatty acids punicic acid and linoleic acid. These fatty acids contain 95% of the oil in pomegranate seeds, of which 99% is triacylglycerol. Other smaller compounds in seed oil include sterols, steroids, tocopherols, and cerebroside (Eikani et al., 2012; Tian et al., 2013; Pirzadeh et al., 2020).

Another part of the pomegranate fruit, which is a rich source of beneficial compounds, is the pomegranate peel. Pomegranate peel is discarded as usual or used as animal feed. But today, a lot of research has been done on the use of this waste material to produce bioactive compounds. About 78% of the waste in pomegranate juice factories is related to the pomegranate peel, so it seems that research in this field is very necessary (Negi et al., 2003; Moghadam et al., 2020). Pomegranate peel contains significant amounts of phenolic compounds such as anthocyanins, ellagic acid, and ellagitannins with promising antioxidant activity (Zivkovic et al., 2018). The most important components of the pomegranate peel are shown in Table 1.

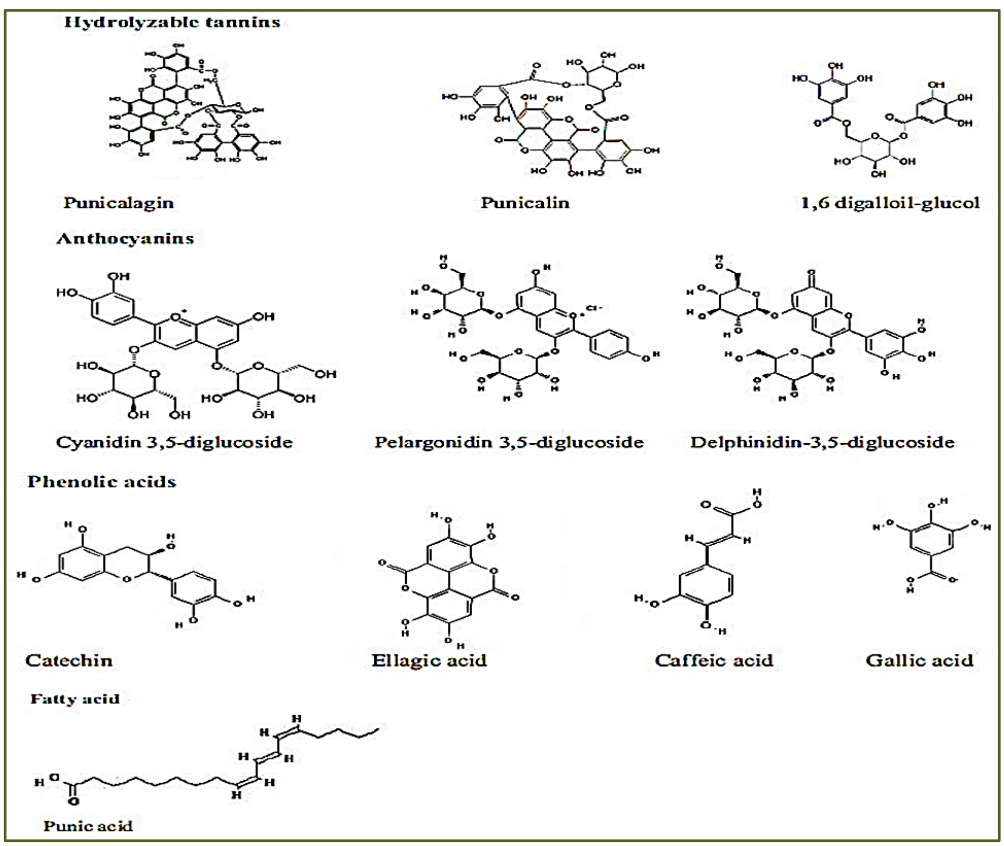

Fig.1. The chemical structure of pomegranate bioactive compounds (reprinted with permission form Vucic et al. 2019).

Table 1. The main bioactive compounds of the pomegranate peel.

Main group	Derivatives
Hydroxybenzoic acid	Gallic acid, ellagic acid
Hydroxycinnamic acid	Caffeic acid, clorogenic acid, p-cumaric acid
Flavonoids	Catechin, epicatechin, epigallocatechin-3-galate, quercetin, camphorol, rutin, luteolin, camphorol derivatives and narenginine
Anthocyanins	Cyanidin, pelargonidin and delphinidine
Ellagitannins	Punicalin, punicalagin
Cyclitol carboxylic acid	Quinic acid
AlkaloidS	Pelletierine

3. Extraction of bioactive compounds from pomegranate

Extraction of bioactive compounds from different parts of pomegranate such as peel, seeds, etc. is done by different methods, some of which are mentioned below. The usual method for extracting bioactive compounds from pomegranate is to use different solvents such as water, methanol and ethanol or a mixture of them. Usually in these methods, the amount of extraction efficiency and the amount of antioxidant activity of the extracted compounds depend on the type of solvent, mixture composition, and temperature. However, other methods also have been employed to extract bioactive compounds from pomegranate, the most important of which are ultrasound, membrane, high pressure, microwave, and pressurized liquid methods that can increase the efficiency of extracting bioactive compounds from pomegranate (Rajhaa et al., 2019; Andrade et al., 2019; Sharayei et al., 2019).

Extraction with solvents is a common method to extract bioactive phenolic compounds from pomegranate. In this regard, Sood and Gupta (2015) studied the optimization of bioactive extraction from pomegranate peel using solvent. In their study, ethanol 60% was used as a solvent. After that, the effect of various factors including solid/solvent ratio, temperature, and time on the polyphenol extraction was studied. The optimized condition for the extraction was investigated as following: solid to solvent ratio of 1:30, temperature of 50°C, and time 45 min for extraction. This condition resulted in a yield of 68%, total poly phenolic content of 510 mg gallic acid equivalent/gm, and total flavonoids content of 16.40 mg quercetin/gm. The extracted bioactive compounds also had a DPPH radical scavenging activity of 24.5%.

Membrane-based separation is another method to extract bioactive molecules from pomegranate. Membrane methods can be considered as an alternative to traditional extraction technologies because they have different advantages such as low operating and maintenance costs, moderate temperature and pressure conditions, easy control as well as easy scalability and finally selective separation. In addition, membrane methods do not require special solvents and therefore do not contaminate the extractive active compounds (Castro-Munoz et al., 2019). In this regard, Condid et al. (2017) used ultra-filtration and nano-filtration methods to extract and purify phenolic compounds from pomegranate juice. In this study, flat-sheet ultra- and nano-filtration with molecular weight cut-off of 1000-4000 Da were used to separate bioactive molecules from clarified pomegranate juice. In this work, four types of industrial membranes were employed and the results showed that the membrane with cut-off of 2000 Da had the highest efficiency for the separation of phenolic compounds. The researchers also reported that in all of these membranes, the ability to separate phenolic compounds was much higher than in sugars, and that ultrafiltration and nanofiltration membranes could be used to separate bioactive compounds from pomegranate juice with a high efficiency.

Another method used to extract bioactive compounds from pomegranate is microwave-assisted extraction. Microwave extraction is a method in which a microwave device is used as an energy source. Conventional heating is dependent on the conduction-displacement phenomenon and eventually a large amount of thermal energy is lost through the environment. As for the microwave extraction method, heating is done in a specific and selective path without heat loss in a closed system. This heating mechanism can reduce extraction time compared to the traditional extraction methods (Zheng et al., 2011; Bagada & Patil, 2019). The microwave extraction method is a better alternative to the old (solid-liquid) extraction methods for extracting metabolites from plants. Some of its potential advantages over traditional extraction methods are as follows: 1- Significant reduction in extraction time, duration usually varies from a few seconds to a few minutes (15-20 minutes), 2- Reduction of solvent consumption 3- Improving extraction efficiency, 4- Automatic adjustment of the device which provides more accuracy, 5- Suitability for heat sensitive components, 6- Ability to extract very small (low) components such as heavy metals and pest residues from a few milligrams of the plant sample, and 7- creating turbulence during extraction, which improves the mass transfer phenomenon. One of the disadvantages of this method is that the microwave efficiency is very low and weak when the target compounds are non-polar solvents or when they are volatile (Mandal et al., 2007; Cavdar et al., 2017).

In a study conducted by Zheng et al. (2011), the microwave method was used to extract bioactive molecules from pomegranate peel. By using response surface methodology (RSM), the effects of microwave output power, extraction time, and solid-liquid ratio on total phenolic yield were investigated and the optimal conditions were determined as follows: microwave output power of 600 w, extraction time of 60 s, and solid-liquid ratio of 20. The average experimental phenolic yield under the optimum conditions was found to be 210.36 ± 2.85 mg GAE/g. In the study of Cavdar et al. (2017) also the microwave method was used to extract pomegranate seed oil. RSM was applied to optimize extraction conditions: power (176–300 W), time (5–20 min), particle size (d=0.125– 0.800 mm), and solvent to sample ratio (2:1, 6:1 and 10:1, by mass). The predicted highest extraction yield (35.19%) was obtained using microwave power of 220 W, particle size in the range of d=0.125–0.450 mm, and solvent-to-sample ratio of 10:1 in 5 min extraction time. Moreover, these authors reported that the microwave-assisted solvent extraction resulted in a higher extraction yield than that of Soxhlet (34.70% in 8 h) or cold (17.50% in 8 h) extraction. In addition, it was reported that the amount of phenolic compounds and antioxidant properties of oil produced by microwave method was much better than other methods. In another study, researchers compared microwave and ultrasound methods to extract phenolic compounds from pomegranate peel (Kaderides et al., 2019). The results showed that the microwave method had a yield about 1.7 times higher obtained in a shorter process time (4 min) in comparison to ultrasound-assisted extraction (10 min) suggesting the high efficiency of microwave method for the extraction of biologically active compounds from pomegranate peel.

Ultrasound-assisted extraction is another method to extract phenolic compounds from pomegranate. The sound waves with frequencies above 20 kHz can cause mechanical oscillations in solid, liquid, or gas materials. Unlike electromagnetic waves, sound waves must be propagated in a material and have cycles of expansion and contraction during propagation in the environment. Expansion increases the molecular distance and contraction presses them together. When expanding, bubbles form in a liquid and produce negative pressure. Bubbles form, grow, and eventually disintegrate (cavitation phenomenon). To achieve a suitable ultrasonic extraction, it is necessary to consider some characteristics of plants, such as the amount of moisture, particle size and solvent used for the extraction. In addition, many factors, including frequency, pressure, temperature, and time, affect the mechanism of action of ultrasound (Wang & Weller, 2006). Ultrasonic extraction is a simple method that is a good alternative to the traditional extraction method. The main benefits of using ultrasound in extraction (solid-liquid) include increased extraction efficiency and extraction speed. Ultrasound can reduce the operating temperature and allow the extraction of heat sensitive compounds. Compared to other modem extraction methods such as microwave extraction, the ultrasonic device is cheaper and easier to implement (Vikhu et al., 2008). Ultrasonic extraction similar to Soxhlet extraction can be used with any solvent to extract a wide range of natural compounds. The disadvantages of this method are that the presence of a diffused phase weakens the ultrasound waves and on the other hand the active part of the ultrasound inside the extractor is limited to an area around the ultrasound probe and therefore should be carefully considered in designing of an ultrasound extractor (Turrini et al., 2019). In a study by Zivkovic et al. (2018), the ultrasound method was used to extract phenolic compounds from pomegranate peel. In this study, the influence of extraction time (10–60 min), ethanol concentration (10–90%), solid to solvent ratio (1:10–1:50) and extraction temperature (20–80°C) on total polyphenols content as well on content of individual polyphenolic compounds (ellagic acid, gallic acid, punicalagin and punicalin) was investigated. The optimal extraction process conditions were as follows: extraction time of 25 min, ethanol concentration of 59%, solid to solvent ratio of 1:44, and extraction temperature of 80°C.

Pressurized liquid extraction (PLE) as a method for the extraction of bioactive molecules from pomegranate is an extraction technique where temperature and pressure are used to accelerate extraction of compounds from solid and semi-solid samples. Pressure has been reported to help driving the solvent into the pores of the matrix and enhance the analyte solubility. Since PLE is conducted at elevated pressures, it allows liquid extraction at temperatures above the boiling point of the solvent at atmospheric pressure, thereby improving analyte solubility and its desorption from the matrix. Moreover, the temperature can dramatically modify the relative permittivity of the extracting fluid, increasing its selectivity (Mustafa & Turner, 2011). Pressurized solvent techniques also offer the advantage of enhanced target molecule specificity and speed due to physicochemical properties of the solvent, including density, diffusivity, viscosity and dielectric constant, which can be affected by the pressure and temperature of the extraction system (Carabias-Martinez et al., 2005). In a study carried out by Sumere et al. (2018), pressurized liquids with ultrasound were combined to extract phenolic compounds from pomegranate peel. These methods have advantages compared to the conventional extraction methods, the most important of which are fast, cheap, environmentally friendly, and the use of these methods reduces the degradation of extractive compounds. In addition to the PLE method, ultrasound method was used in the above-mentioned study. Ultrasound causes the phenomenon of cavitation in which the accumulation of energy causes waves in the solvent that increase their penetration into the sample tissues. In this study, the effects of several variables of the process on extraction yield, including solvent type (water, ethanol + water 30, 50 and 70% v:v), temperature (50–100°C), ultrasound power (0–800 W at the generator, or 0–38.5 W at the tip of the probe), mean particle size (0.68 and 1.05 mm), and number of cycles (1–5), were analyzed according to the yield of 20 different phenolic compounds. It should also be noted that the amount of pressure used in this study to produce pressurized solvents was equal to 10 MPa. The optimal conditions for extracting phenolic compounds in this study were 70-80°C and 480-640W ultrasound, which were more effective at larger particle sizes. The researchers also reported that the extraction process in the presence of ultrasound was faster. In another study, also the PLE method was used to extract polyphenols from pomegranate peel (Cam & Hisil, 2010). The researchers compared extraction with pressurized water with extraction with methanol and stated that pressurized water had a higher ability to extract polyphenols from pomegranate peel. In another study, it was stated that the use of an expansion gas in a pressurized system can increase the extraction of bioactive compounds from pomegranate. Therefore, the researchers used nitrogen gas in the liquid system under pressure-ultrasound as an expansion gas and stated that the use of this gas increased the extraction efficiency of bioactive compounds from pomegranate by 20% (Santos et al., 2019).

4. Conclusion

Pomegranate is a very ancient plant with a medicinal history that research on its healing properties has increased in the recent decades. Bioactive compounds in different parts of this plant such as peels, seeds, and juice have excellent health-promoting properties such as antioxidant, antimicrobial, and anti-cancer activities. Therefore, this fruit can be mentioned as a super fruit and can be used for medicinal purposes or in the production of functional foods with improved health-promoting attributes. However, in order to achieve the valuable properties of bioactive compounds of pomegranate, it is necessary to extract these compounds from the fruit. In this regard, different methods have been employed such as extraction with solvents, extraction with pressurized liquids, and ultrasound-assisted extraction. The extraction efficiency and the bioactivity of the extracted compounds are dependent on different factors such as time and temperature of the extraction process. Therefore, it seems that new methods need to be developed to extract bioactive compounds from pomegranate, and therefore more comprehensive studies are required to reach this purpose.

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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